UNITED STATES PATENT OFFICE.

HERMANN THOMS, OF BERLIN, GERMANY.

PROCESS OF MAKING PARA-PHENETOL CARBAMIDE.

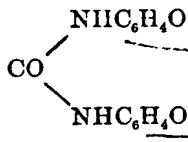
SPECIFICATION forming part of Letters Patent No. 502,504, dated August 1, 1893.

Application filed November 18, 1892. Serial No. 452,446. (Specimens.)

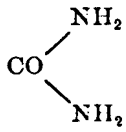
To all whom it may concern:

Be it known that I, HERMANN THOMS, chemist, a subject of the Emperor of Germany, residing in the city of Berlin, German Empire, have invented certain new and useful Improvements in the Production of Para Phenetol Carbamide; and I do hereby declare that the following is a full, clear, and exact description of the invention, such as will enable others skilled in the art to which it appertains to make and use the same.

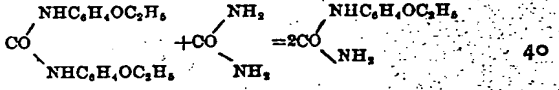
My previous researches (published in the *Pharm. Centralhalle*, March 24, 1892,) have shown that di-para-phenetylurea



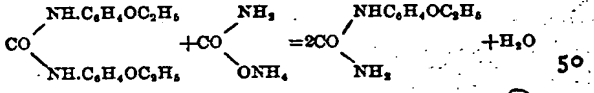
may be readily obtained, in addition to the hydrochlorid of phenetidin, by causing carbonylchlorid to act on a solution of para phenetidin in toluene. Since then I have found that this body, when heated for several hours with common urea



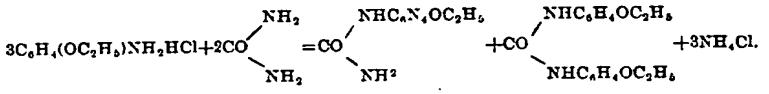
in equimolecular proportions in a closed vessel, and at a temperature ranging between 150° and 160° centigrade, is easily converted into the para phenetol carbamide as indicated by the following equation:—



Instead of the common urea the carbamide salt of ammonia or commercial ammonium carbonate may be employed. The reaction takes place in the first case as indicated by the following equation:



I have found also, that instead of the di-paraphenetylurea, paraphenetidin or the hydrochlorid of para-phenetidin may be employed, the latter being either treated in a closed vessel with common urea, or the carbamide salt of ammonia, or with commercial ammonium carbonate at a temperature of 160° centigrade; or an aqueous solution of the hydrochlorid of the paraphenetidin (three molecules) and common urea (two molecules) being heated and kept at the boiling point for a considerable time, the reaction being indicated by the following equation:



This process will yield, in addition to the para-phenetol carbamide, diparaphenetylurea. The paraphenetolcarbamide crystallizes from the hot filtrate.

The paraphenetolcarbamide obtained as described from diparaphenylurea, or from paraphenetidin by the action of common urea or the carbamide salt of ammonia, or commercial ammonium carbonate, melts at a temperature approaching 170° centigrade, and has a sweet taste of extraordinary intensity which renders it suitable for industrial application as a sweetening substance. According to physiological experiments, the new substance is quite harmless to the human organism.

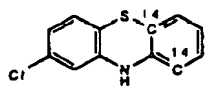
Having thus described my invention, what I claim as new therein, and desire to secure by Letters Patent, is—

1. The process of obtaining paraphenetol carbamide, by the reaction of a para salt of phenetidin on a substance such as common urea in about the proportions set forth.

2. The process of obtaining para-phenetolcarbamide, which consists in boiling an aqueous solution of para-phenetidin-hydrochlorid with common urea in about the proportions set forth.

HERMANN THOMS.

Witnesses:
FRITZ RINDEL,
AUG. FRAHNE.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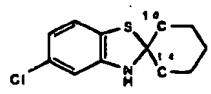
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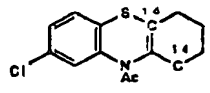
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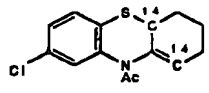
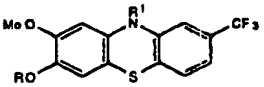

IV

to give the tetrahydrophenothiazine olefin mixt. III and IV which was directly converted to labeled II via treatment with DDQ in refluxing benzene followed by hydrolysis of the acetyl group.

91: 74554j Synthesis of 7,8-disubstituted metabolites of triflupromazine: 2-(trifluoromethyl)-7,8-dimethoxy-10-[3-(dimethylamino)propyl]-phenothiazine and related compounds. Mital, R. L.; Mittal, Madhu; Laxmi, V.; Mittal, Suresh; Shukla, A. P. (Dep. Chem., Univ. Rajasthan, Jaipur, 302 004 India). *J. Inst. Chem. (India)* 1978, 50(4), 159–61 (Eng). Phenothiazine I [R = Me, $R^1 = (CH_2)_3NMe_2$], a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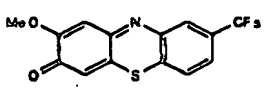
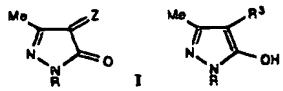

II

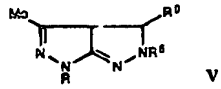
metabolite of triflupromazine was prepd. Thus, condensation of 2,4-$H_2N(F_3C)C_6H_3SH$ Zn salt with 2-chloro-5-methoxy-*p*-benzoquinone in refluxing EtOH 4 h gave II quant., II was reduced with $Na_2S_2O_4$ in aq. Me_2CO to give 90% phenothiazinol I (R = R^1 = H). The product was *O*-methylated with Me_2SO_4 in Me_2CO contg. $Na_2S_2O_4$ and aq. KOH 4h at 60° and the product ether I (R = Me, R^1 = H) (67% yield) was *N*-alkylated by $Cl(CH_2)_3NMe_2$ in Me_2SO contg. NaH 2 h at room temp. to give I [R = Me, $R^1 = (CH_2)_3NMe_2$], characterized as its maleate.

DIAZINES

91: 74555k Reactions of 3-methyl-1-aryl-Δ²-pyrazolin-5-ones with aromatic aldehydes, aryldiazonium chlorides and of their products 3-methyl-1-aryl-4-arylidene-Δ²-pyrazolin-5-ones with secondary amines, hydrazines, dialkyl phosphites, Grignard reagents, ethyl aceto- or cyanoacetate and cyclohexanone. Zimaity, T.; Afsah, E.; Abbas. M. (Fac. Sci., Mansoura Univ., Mansoura, Egypt). *Indian J. Chem., Sect. B* 1978, 16B(10), 876–9 (Eng). Reactions of I (R = *p*-ClC_6H_4,

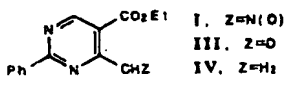

I

IV


V

p-$O_2NC_6H_4$; Z = H_2 (II) with R^1CHO (R^1 = *p*-$MeOC_6H_4$, $O_2NC_6H_4$, $Me_2NC_6H_4$; thienyl) gave I (Z = CHR^1) (III). II and *p*-$ClC_6H_4N_2Cl$ gave I (Z = H, N:NC_6H_4Cl-*p*). Mannich reaction of II gave I (Z = H, R^2NHCH_2; R^2 = *p*-ClC_6H_4, Me). III and piperidine gave IV (R^3 = *p*-$MeOC_6H_4CHR^4$, R^4 = piperidino, etc.). Cyclization of III with N_2H_4 and $PhNHNH_2$ gave V (R^5 = Ph, H: R^6 = *p*-$MeOC_6H_4$ etc.). Reactions of II with dialkyl phosphite, Grignard reagents, Et acetoacetate, $NCCH_2CO_2Et$ and cyclohexanone gave compds. related to I and IV.

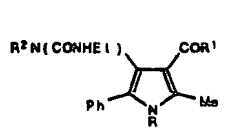
91: 74556m Synthesis and biological activity of α-(5-ethoxycarbonyl-2-phenyl-4-pyrimidinyl)-N-substituted nitrones. Roy, S. K.; Rao, K. Srinivasa; Reddi, G. S.; Sachdeva, Meena (Res. Dev. Dep., Indian Drugs and Pharm. Ltd., Hyderabad, India). *Indian J. Chem., Sect. B* 1978, 16B(10), 907–9 (Eng).

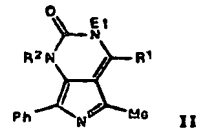

I, Z=N(O)R
III, Z=O
IV, Z=H₂

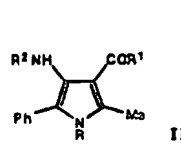
Title compds. I (R = Et, Pr, Bu, CH_2CH_2OH, Ph, $PhCH_2$, *o*-MeC_6H_4, *p*-ClC_6H_4 (II), *p*-$MeSO_2C_6H_4$) were prepd. by treating RNHOH with pyrimidinecarboxaldehyde III, which was prepd. by Kroehnke oxidn. of IV. I at 25–200 μg/mL were fungicidal against dematophytes. II killed *Mycobaterium tuberculosis* at 25 μg/mL.

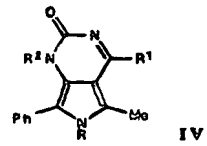
91: 74557n Pyrimidines. Part LXXVI. tert-Butylation of quinazoline. De Bie, D. A.; Nagel, A.; Van der Plas, H. C.; Geurtsen, G.; Koudijs, A. (Lab. Org. Chem., Agric. Univ., Wageningen, Neth.). *Tetrahedron Lett.* 1979, (7), 649–52 (Eng). Quinazoline (I) is present in soln. at pH 3 as its cationic covalent hydrate; and treatment of an aq. soln. of I with excess Me_3CCO_2H and ammonium peroxydisulfate, in the presence of a catalytic amt. of $AgNO_3$ at 40° and at pH 1, gave 2-*tert*-butyl-3,4-dihydro-4-oxoquinazoline (II), quant. Similar treatment of I at 70° and at pH 5 for 2 h gave a 4:3:2 mixt. of 2-*tert*-butylquinazoline (III), 4-*tert*-butylquinazoline (IV), and 2,4-di-*tert*-butylquinazoline (V), whereas similar treatment of I at 70° and at pH 4 gave mainly 2-$HCOC_6H_4NHCHO$ and 2-$HCOC_6H_4NH_2$ (VI). At pH 3, VI was the main product together with III, IV, V, and 4-*tert*-butyl-3,4-dihydroquinazoline. The formation of II, III, IV, V, and VI is discussed.

91: 74558p Synthesis and antiinflammatory properties of some pyrrolo(1H,3H)[3,4-d]pyrimidin-2-ones and pyrrolo(1H,6H)[3,4-d]pyrimidin-2-ones. Tarzia, G.; Panzone, G.; Schiatti, P.; Selva, D. (Dep. Org. Chem., Lepetit Res. Lab., Milan, Italy). *Farmaco, Ed. Sci.* 1979, 34(4), 316–30 (Eng).


I

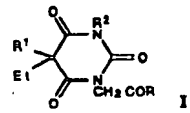

II


III


IV

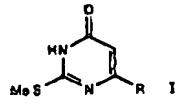
The cyclocondensation reaction of pyrroles II (R = H, Me, Et; R^1 = Me, Ph; R^2 = Et, H, $CHMe_2$) in MeOH contg. HCl yielded pyrrolopyrimidinones II, and III (R, R^1, and R^2 same as above), which reacted with NaOCN at room temp. to give IV; II and IV exhibited antiinflammatory activity. III (R = R^2 = Et, R^1 = Me) in HOAc was added to NaOCN in H_2O, and the mixt. was kept 4 h at room temp. to give IV (R = R^2 = Et, R^1 = Me).

91: 74559q Synthesis and pharmacological screening of some N-carboxymethylbarbituric acid derivatives. I. Mirek, Julian; Adamczyk, Maciej; Chojnacka-Wojcik, Ewa; Naparzewska, Anna (Inst. Chem., Jagellonian Univ., 30-060 Krakow, Pol.). *Pol. J. Pharmacol. Pharm.* 1978, 30(5), 685–93 (Eng). Methylphenobarbital or barbital were *N*-alkylated with


I

$ClCH_2CO_2Me$ or $BrCH_2CO_2Et$ in PhMe contg. K_2CO_3 to give 87–90% carbalkoxy derivs. I (R = OMe, OEt, R^1 = Ph, R^2 = Me) or 85–6% I (R = OMe, R^2 = CH_2CO_2Me, R = OEt, R^2 = CH_2CO_2Et, R^1 = Et). Hydrolysis of these esters with refluxing concd. HCl gave 90% II (R = OH, R^1 = Ph, R^2 = Me) or 95% I (R = OH, R^1 = Et, R^2 = CH_2CO_2H) which were converted into 95% the corresponding acid chlorides with $SOCl_2$. I (R = Cl, R^1 = Ph, R^2 = Me) was treated with 2 mol-equiv amines to give 82–90% amides I (R = 2-, 4-$HO_2CC_6H_4NH$, 3-pyridylamino, 4-pyridylmethylamino). I (R = Cl, R^1 = Et, R^2 = CH_2COCl) was treated with 4 mol-equiv amines to give 89–92% diamides I (R = 2-, 4-$HO_2CC_6H_4NH$, 3-pyridylamino, 4-pyridylmethylamino, morpholino; R^1 = $RCOCH_2$). The amides had no anticonvulsant activity and showed only slight sedative and analgesic action.

91: 74560h Photolysis of thiopyrimidine derivatives. Part II. 2-(Methylthio)-6-methyluracil and 2-(methylthio)-6-ethyluracil. Golankiewicz, Krzysztof; Szajda, Maria; Wyrzykiewicz, Elzbieta (Inst. Chem., A. Mickiewicz Univ., 60780 Poznan, Pol.). *Pol. J. Chem.* 1979, 53(2), 529–31 (Eng). Irradn. of I (R = Me,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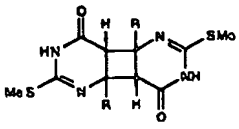
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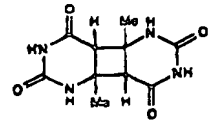
III

Et) in Me_2CO at λ >254 nm gives 20.5% II (R = Me, Et); irradn. of aq. II at 254 nm gave I. The hydrolysis of II (R = Me) gave III which on irradn. (in acidic, basic, or neutral H_2O) at 254 nm gave 6-methyluracil; this established the anti-configuration for II (R = Me). The photodimerization of I (R = alkyl) was contrasted to the lack of photodimerization of I (R = CO_2H).

91: 74561j Succinate dehydrogenase inhibitory activity of new 1-aryl-3-(N,N-dimethylaminopropyl) thiobarbiturates. Tripathi, Shephali; Pandey, B. R.; Raman, K.; Barthwal, J. P.; Kisher, K.; Bhargava, K. P. (King Georg's Med. Coll., Lucknow Univ., Lucknow, India). *Eur. J. Med. Chem. – Chim. Ther.* 1979, 14(2), 133–4 (Eng). Thiobarbiturates I (R = Ph, isomeric tolyl, xylyl, or anisyl, 2-$EtOC_6H_4$, 2- or 4-ClC_6H_4, 4-BrC_6H_4) were prepd. by treating $Me_2NCH_2CH_2CH_2NH_2$ with RNCS and cyclocondensing product thioureas $Me_2NCH_2CH_2CH_2NHC(S)NHR$ with malonic acid. I inhibited (15.1–75.50%) succinate dehydrogenase in vitro activity of rat brain homogenate.